

AMENDMENTS TO THE CLAIMS:

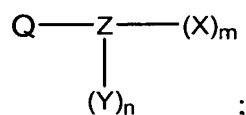
This listing of claims, in accordance with the revision of 37 C.F.R §1.121, is provided. Please amend claims 1, 2, 150, 161, 166, and 173. Please cancel claim 170 without prejudice or disclaimer. This listing of claims replaces all prior versions and listings of claims in the application.

LISTING OF CLAIMS:

1. (Currently Amended) A method, comprising:

(a) contacting a capture compound with a sample comprising biomolecules to effect capture of biomolecules in the sample, wherein:

the capture compound has the formula:



X is selected to covalently bind to biomolecules or to bind with sufficiently high affinity so that the resulting complexes of biomolecule/capture compounds are stable under conditions of mass spectrometric analysis;

Y is a pharmaceutical drug, drug fragment, drug intermediate, drug metabolite or prodrug;

Q is a sorting function;

Z is a moiety for presenting ~~X and Y~~; X, Y and Q;

m is an integer that is 1 to 100;

n is an integer from 1 to 100; and

contacting is effected for a sufficient time for the interaction between the capture compounds and the biomolecules to reach equilibrium, wherein the interaction with Y and a biomolecule reaches equilibrium;

(b) forming a covalent linkage or high affinity bond between X and the biomolecule to effect capture thereof; and

(c) isolating and identifying the captured biomolecules to thereby identify biomolecules that interact with moiety Y.

[[.]] 2. (Currently Amended) The method of claim 1, wherein the captured biomolecules comprise drug targets and non-targets, whereby drug non-targets are identified.

Claims 3-4 (Cancelled).

5. (Previously Presented) The method of claim 1 wherein, the moiety Y is linked to the moiety Z in different orientations via different points of attachments on the Y moiety.

6. (Original) The method of claim 1, wherein the biomolecules are proteins.

Claims 7-9 (Cancelled).

10. (Original) The method of claim 1, wherein Q permits separation of capture compounds by arraying of the capture compounds on a solid support by binding to the surface or a molecule thereon.

Claims 11-14 (Cancelled).

15. (Previously Presented) The method of claim 1, wherein Z is a moiety that is cleavable prior to or during mass spectrometric analysis of biomolecules bound to the capture compound.

Claim 16 (Cancelled).

17. (Previously Presented) The method of claim 1, wherein Z is a moiety that is not cleavable prior to or during mass spectrometric analysis of biomolecules bound to the capture compound.

18. (Previously Presented) The method of claim 1, wherein:

Q is an oligonucleotide or oligonucleotide analog that includes a single-stranded portion of sufficient length "j" to form a stable hybrid with a base-complementary single stranded nucleic acid molecule or analog.

Claims 19-21 (Cancelled).

22. (Previously Presented) The method of claim 1, wherein Q has the formula $N^1_s B_i N^2_u$, wherein:

N^1 , B and N^2 are oligonucleotides or oligonucleotide analogs comprising s, t and u members, respectively;

B is a region of sequence permutations that contains at least two bases; and sum of s, i and u is at least 5.

Claims 23 and 24 (Cancelled).

25. (Original) The method of claim 1, wherein Z is a photocleavable, acid cleavable, alkaline cleavable, oxidatively cleavable, or reductively cleavable group.

Claims 26-33 (Cancelled).

34. (Previously Presented) The method of claim 1, wherein Z has the formula:

$(S^1)_t M(R^{15})_a (S^2)_b L$, wherein:

S^1 and S^2 are spacer moieties;

t and b are each independently 0 or 1;

a is an integer from 0 to 4;

M is a central moiety possessing three or more points of attachment;

R^{15} is a monovalent group independently selected from $Y^2 R^{18}$;

Y^2 is a divalent group independently having any combination of the following groups: a direct link, arylene, heteroarylene, cycloalkylene, $>C(R^{17})_2$, $C(R^{17})=C(R^{17})$, $>C=C(R^{23})(R^{24})$, $>C(R^{23})(R^{24})$, $C\equiv C$, O, $>S(A)_u$, $>P(D)_v(R^{17})$, $>P(D)_v(ER^{17})$, $>N(R^{17})$, $>N(COR^{17})$, $>N^+(R^{23})(R^{24})$, $>Si(R^{17})_2$ and $>C(E)$; where u is 0, 1 or 2; v is 0, 1, 2 or 3; A is O or NR^{17} ; D is S or O; and E is S, O or NR^{17} ;

R^{17} and R^{18} are each independently selected from the group consisting of hydrogen, halo, pseudohalo, cyano, azido, nitro, $SiR^{27}R^{28}R^{25}$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy and $NR^{19}R^{20}$;

R^{19} and R^{20} are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl and heterocyclyl;

R^{23} and R^{24} are selected from (i) or (ii) as follows:

(i) R^{23} and R^{24} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; or

(ii) R^{23} and R^{24} together form alkylene, alkenylene or cycloalkylene;

R^{25} , R^{27} and R^{28} are each independently a monovalent group selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy and $NR^{19}R^{20}$;

R^{15} , R^{17} , R^{18} , R^{19} , R^{20} , R^{23} , R^{24} , R^{25} , R^{27} and R^{28} can be substituted with one or more substituents each independently selected from Z^2 ; Z^2 is selected from alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, hydroxy, $S(O)_hR^{35}$; h is 0, 1 or 2, $NR^{35}R^{36}$, $COOR^{35}$, COR^{35} , $CONR^{35}R^{36}$, $OC(O)NR^{35}R^{36}$, $N(R^{35})C(O)R^{36}$, alkoxy, aryloxy, heteroaryl, heterocyclyl, heteroaryloxy, heterocyclyoxy, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, aralkoxy, heteroaralkoxy, alkoxycarbonyl, carbamoyl, thiocarbamoyl, alkoxycarbonyl, carboxyaryl, halo, pseudohalo, haloalkyl and carboxamido;

R^{35} and R^{36} are each independently selected from among hydrogen, halo, pseudohalo, cyano, azido, nitro, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy, amino, amido, alkylamino, dialkylamino, alkylaryl amino, diarylamino and arylamino; and

L is a group that is cleavable prior to or during mass spectrometric analysis of the compound.

Claims 35-37 (Cancelled).

38. (Original) The method of claim 34, wherein L is a disulfide moiety, a photocleavable group, an acid cleavable group, an alkaline cleavable group, a oxidatively cleavable group, or a reductively cleavable group.

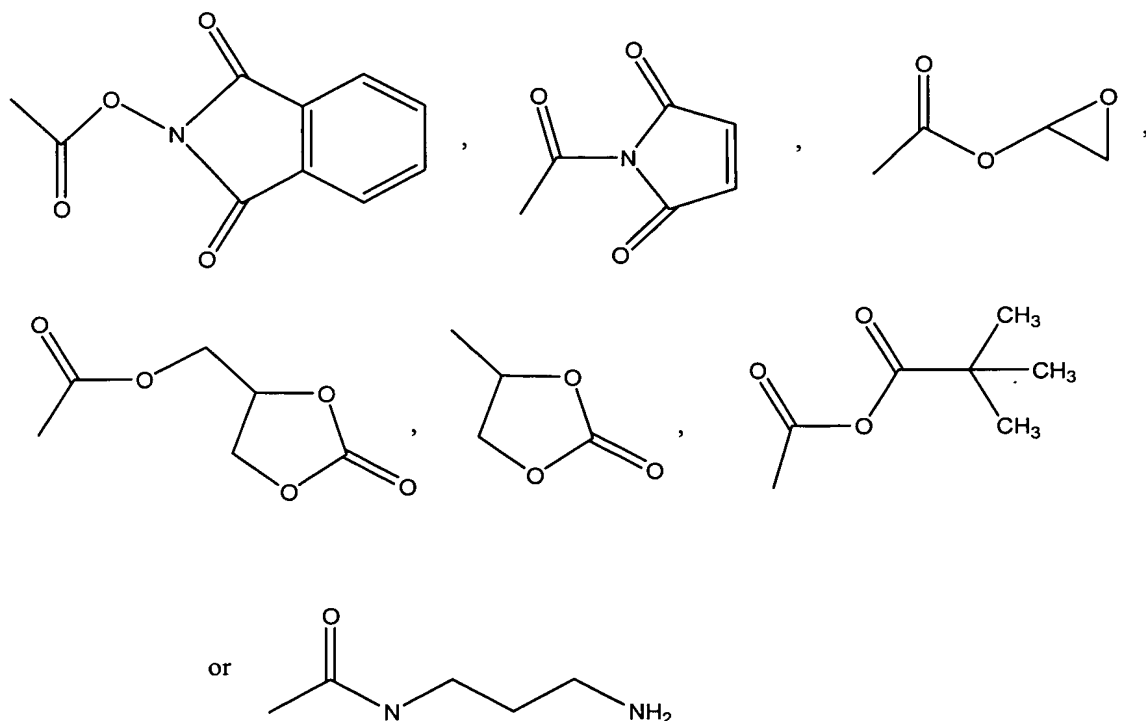
Claims 39-42 (Cancelled).

43. (Previously Presented) The method of claim 1, wherein each X is selected from the group consisting of an active ester, an active halo moiety, an amino acid side chain-specific functional group, and a specific peptide that binds to a biomolecule surfaces.

44. (Previously Presented) The method of claim 1, wherein an X is an α -halo ether, an α -halo carbonyl group, maleimido, a metal complex, an expoxide, and an isothiocyanate.

Claim 45 (Cancelled).

46. (Original) The method of claim 1, wherein X is



47. (Previously Presented) The method of claim 1, wherein the capture compounds comprise a mass modifying tag linked to Z.

Claims 48-54 (Cancelled).

55. (Previously Presented) The method of claim 18, wherein capture compounds are hybridized to a plurality of oligonucleotides or analogs thereof that comprise oligonucleotides that are complementary to each Q.

56. (Original) The method of claim 55, wherein the oligonucleotides or analog thereof that are complementary to Q are immobilized on a solid support as an array.

Claims 57-62 (Cancelled).

63. (Currently amended) The method of claim 1, wherein the Z moiety of the capture compound comprises a functionality conferring luminescence, fluorescence, chemiluminescence or colorimetric properties.

Claims 64 and 65 (Cancelled).

66. (Original) The method of claim 1, wherein the capture compounds further comprise a solubility group W that influences the solubility properties of the capture compound.

67. (Previously Presented) The method of claim 1, wherein the selectivity function Y is a drug or drug intermediate/fragment selected from among those set forth in Figure 17 and Figure 21.

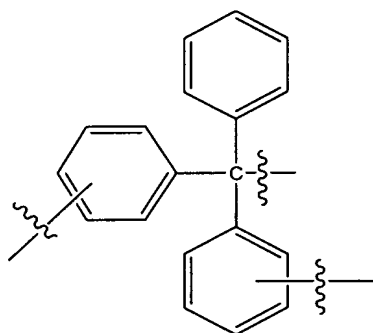
68. (Previously Presented) The method of claim 1, wherein the reactivity function X is selected from those set forth in Figure 16.

Claims 69-74 (Cancelled).

75. (Previously Presented) The method of claim 1, wherein Q is biotin.

Claim 76 (Cancelled).

77. (Previously Presented) The method of claim 1, wherein Z has the formula:



78. (Previously Presented) The method of claim 132, wherein X is selected from the groups set forth in Figure 16.

79. (Previously Presented) The method of claim 132, wherein Y is selected from the groups set forth in Figure 17.

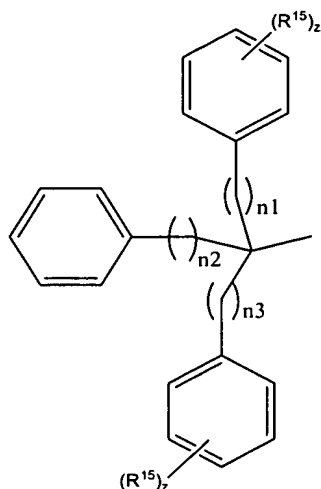
Claim 80 (Cancelled).

81. (Previously Presented) A collection of capture compounds, comprising a plurality of capture compounds, wherein each set of capture compounds includes:

a moiety X that is selected to covalently bind to biomolecules or to bind with sufficiently high affinity so that the resulting complexes of biomolecule/capture compounds are stable under conditions of mass spectrometric analysis;

a moiety Y that increases the selectivity of the binding by X such that the capture compound binds to fewer biomolecules when the selectivity moiety is present than in its absence; and

a moiety Z for presenting X and Y, wherein the moiety Z is



wherein R¹⁵ is H, OH, OR⁵¹, SH, SR⁵¹, NH₂, NHR⁵¹, N(R⁵¹)₂, F, Cl, Br, I, SO₃H, PO₄, CH₃, CH₂CH₃, CH(CH₃)₂ or C(CH₃)₃; where R⁵¹ is straight or branched chain alkyl, straight or branched chain alkenyl, straight or branched chain alkynyl, aryl, heteroaryl, cycloalkyl, heterocyclyl, straight or branched chain aralkyl, straight or branched chain aralkenyl, straight or branched chain aralkynyl, straight or branched chain heteroaralkyl, straight or branched chain heteroaralkenyl, straight or branched chain heteroaralkynyl, straight or branched chain cycloalkylalkyl, straight or branched chain cycloalkylalkenyl, straight or branched chain cycloalkylalkynyl, straight or branched chain heterocyclylalkyl, straight or branched chain heterocyclylalkenyl or straight or branched chain heterocyclylalkynyl;

z is an integer from 1 to 4; and

n₁, n₂, n₃ are 0 to 4 with the proviso that all n₁, n₂ and n₃ are not equal to 0 at the same time.

82.-109. (Cancelled)

110. (Previously Presented) The method of claim 1, further comprising identifying or detecting a captured biomolecule by mass spectrometric analysis.

Claims 111-115 (Cancelled).

116. (Previously Presented) The method of claim 1, wherein the sample comprises a biological sample, a body tissue or fluid or a cell lysate.

Claim 117 (Cancelled).

118. (Original) A system for analysis of mixtures of biomolecules, comprising:
a collection of capture compounds of claim 81;

a computer programmed with instructions for controlling and directing analysis of biomolecules using the collections;

a mass spectrometer; and

software for analysis of data produced by the mass spectrometer.

Claim 119 (Cancelled).

120. (Previously Presented) The system of claim 118, further comprising a liquid chromatographic device.

Claims 121-136 (Cancelled).

137. (Previously Presented) The method of claim 1, wherein Z has the formula:

$(S^1)_t M(R^{15})_a (S^2)_b$, wherein:

S^1 and S^2 are spacer moieties;

t and b are each independently 0 or 1;

a is an integer from 0 to 4;

M is a central moiety possessing three or more points of attachment;

R^{15} is a monovalent group independently selected from $Y^2 R^{18}$;

Y^2 is a divalent group independently having any combination of the following groups: a direct link, arylene, heteroarylene, cycloalkylene, $>C(R^{17})_2$, $C(R^{17})=C(R^{17})$, $>C=C(R^{23})(R^{24})$, $>C(R^{23})(R^{24})$, $C\equiv C$, O, $>S(A)_u$, $>P(D)_v(R^{17})$, $>P(D)_v(ER^{17})$, $>N(R^{17})$, $>N(COR^{17})$, $>N^+(R^{23})(R^{24})$, $>Si(R^{17})_2$ and $>C(E)$; wherein:

u is 0, 1 or 2;

v is 0, 1, 2 or 3;

A is O or NR^{17} ;

D is S or O; and

E is S, O or NR^{17} ;

R^{17} and R^{18} are each independently selected from the group consisting of hydrogen, halo, pseudohalo, cyano, azido, nitro, $SiR^{27}R^{28}R^{25}$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy and $NR^{19}R^{20}$;

R¹⁹ and R²⁰ are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl and heterocyclyl;

R²³ and R²⁴ are selected from (i) or (ii) as follows:

(i) R²³ and R²⁴ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl and heteroaryl; or

(ii) R²³ and R²⁴ together form alkylene, alkenylene or cycloalkylene;

R²⁵, R²⁷ and R²⁸ are each independently a monovalent group selected from hydrogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy and NR¹⁹R²⁰;

R¹⁵, R¹⁷, R¹⁸, R¹⁹, R²⁰, R²³, R²⁴, R²⁵, R²⁷ and R²⁸ can be substituted with one or more substituents each independently selected from Z²; Z² is selected from alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, hydroxy, S(O)_hR³⁵; h is 0, 1 or 2, NR³⁵R³⁶, COOR³⁵, COR³⁵, CONR³⁵R³⁶, OC(O)NR³⁵R³⁶, N(R³⁵)C(O)R³⁶, alkoxy, aryloxy, heteroaryl, heterocyclyl, heteroaryloxy, heterocycliloxy, aralkyl, aralkenyl, aralkynyl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, aralkoxy, heteroaralkoxy, alkoxycarbonyl, carbamoyl, thiocarbamoyl, alkoxycarbonyl, carboxyaryl, halo, pseudohalo, haloalkyl and carboxamido; and

R³⁵ and R³⁶ are each independently selected from among hydrogen, halo, pseudohalo, cyano, azido, nitro, trialkylsilyl, dialkylarylsilyl, alkyl diarylsilyl, triarylsilyl, alkyl, alkenyl, alkynyl, haloalkyl, haloalkoxy, aryl, aralkyl, aralkenyl, aralkynyl, heteroaryl, heteroaralkyl, heteroaralkenyl, heteroaralkynyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heterocyclylalkynyl, hydroxy, alkoxy, aryloxy, aralkoxy, heteroaralkoxy, amino, amido, alkylamino, dialkylamino, alkylaryl amino, diarylamino and arylamino.

Claim 138 (Cancelled).

139. (Original) The method of claim 1, wherein X is a photoactivatable group.

140. (Original) The method of claim 139, wherein the capture compound interacts with the biomolecule mixture prior to activation of the photoactivatable group.

Claims 141 and 142 (Cancelled).

143. (Previously Presented) The method of claim 1, further comprising

re-designing the moiety Y to eliminate or alter its binding interactions with a captured biomolecule.

144. (Previously Presented) The method of claim 1, further comprising identifying a function of a captured biomolecule.

145. (Original) The method of claim 143, wherein the alteration in binding is an increase in binding.

146. (Original) The method of claim 143, wherein the alteration in binding is a decrease in binding.

147. (Original) The method of claim 143, wherein the biomolecule for which binding is altered is a non-target biomolecule.

Claims 148 and 149 (Cancelled).

150. (Currently Amended) The method of claim 1, wherein X is a latent reactivity group requiring activation following contacting with the biomolecules to allow for ~~reaction of the Y group with the biomolecules~~ covalent binding of the capture compound to the biomolecule.

151. (Previously Presented) The method of claim 1, wherein the sample is contacted with a collection of capture compounds.

152. (Previously Presented) The method of claim 1, wherein the X moiety of the capture compound comprises an azide, diazirine or a group which, following activation, reacts with the biomolecule.

153. (Previously Presented) The method of claim 143, wherein the method is repeated with the re-designed moiety Y linked to a capture compound to effect further modification thereof.

Claim 154 (Cancelled).

155. (Previously Presented) The method of claim 143, wherein the captured biomolecule for which binding is altered is a drug target protein.

156. (Previously Presented) The method of claim 143, wherein the captured biomolecule for which binding is altered is a non-drug target protein.

157. (Previously Presented) The method of claim 6, wherein the contacting step is performed under conditions whereby the interactions of the moiety Y with proteins in the sample reaches equilibrium.

158. (Original) The method claim 157, wherein after equilibrium the mixture is treated to form a covalent bond between the capture agent and the proteins.

159. (Previously Presented) The method of claim 158, wherein the treatment comprises a change in pH.

160. (Previously Presented) The method of claim 1, wherein a concentration of capture compound is varied in a plurality of different reactions.

161. (Currently Amended) The method of claim 160, wherein a ~~dissolution~~ dissociation constant (~~Kd~~) value (Kd value) is determined.

Claim 162 (Cancelled).

163. (Previously Presented) The method of claim 110, wherein the mass spectrometry format is selected from among matrix assisted laser desorption ionization (MALDI), continuous or pulsed electrospray (ES) ionization, ionspray, thermospray, and massive cluster impact mass spectrometry.

164. (Original) The method of claim 163, wherein the detection format is linear time-of-flight (TOF), reflectron time-of-flight, single quadrupole, multiple quadrupole, single magnetic sector, multiple magnetic sector, Fourier transform, ion cyclotron resonance (ICR), or ion trap.

Claim 165 (Cancelled).

166. (Currently Amended) The method of claim 144, wherein the function of the biomolecule is determined by sequence alignment, pharmacophores, homology models and protein motif correlation, liver ~~microsomes~~ microsomes metabolic pathways, cDNA-expressed enzymes, signal pathways and back-mapping to yeast pathways, simulations and protein/protein interaction of pull-out proteins, native polymorphisms, knock-out/knock-in, flow cytometry, therapeutic activity of the drug, or prospective genotyping and prospective phenotyping.

167. (Previously Presented) The method of claim 143, wherein:

the moiety Y is a first drug; and

redesigning the first drug results in a second drug with fewer side-effects or an increased therapeutic index as compared to the first drug.

168. (Previously Presented) The method of claim 1, wherein the drug is selected from among troglitazone, rosiglitazone, pioglitazone, methotrexate, atorvastatin, celecoxib, refecoxib and cerivastatin.

169. (Previously Presented) The method of claim 158, wherein the treatment comprises activation with light.

170. (Cancelled)

171. (Previously Presented) The method of claim 22, where B is a single stranded DNA or RNA and the number of sequence permutations is equal to 4^i , wherein i is about 2 to about 25.

172. (Previously Presented) The method of claim 172, where i is about 3 to about 5, 6, 7 or 8.

173. (Currently Amended) The method of ~~claim 133~~, claim 1, wherein the moiety Y is selected from among a receptor ligand, an enzyme substrate, an enzyme inhibitor, a co-factor, a transition state analog, and a peptide selected to increase the selectivity of the binding by X such that the capture compound binds to fewer biomolecules when the selectivity moiety Y is present than in its absence.